# ปัจจัยที่สัมพันธ์กับผลการรักษาวัณโรคที่ไม่พึงประสงค์ภายใต้รูปแบบการทำ DOT ที่ไม่ใช้ญาติผู้ป่วย: การศึกษาแบบ retrospective cohort

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**บทคัดย่อ**

การศึกษา retrospective cohort นี้มีวัตถุประสงค์เพื่อหาปัจจัยที่สัมพันธ์กับผลการรักษาวัณโรคที่ไม่พึงประสงค์ของโรงพยาบาลท่าศาลา จังหวัดนครศรีธรรมราช ซึ่งเป็นโรงพยาบาลขนาด 120 เตียง ที่ได้ดำเนินงานใช้รูปแบบการรักษาผู้ป่วยวัณโรคภายใต้การสังเกตการรับประทานยาต่อหน้าพี่เลี้ยงที่ไม่ใช่ญาติผู้ป่วยมาตั้งแต่ปี 2550 ผู้ป่วยวัณโรครายใหม่จำนวนทั้งหมด 955 รายซึ่งขึ้นทะเบียนรักษาตั้งแต่ปี 2550 - 2557 ได้รับการทบทวนประวัติการรักษาวัณโรค แต่มีจำนวน 49 รายได้ถูกตัดออกจากการศึกษาด้วยเหตุผลส่วนใหญ่จากการเปลี่ยนแปลงการวินิจฉัย กลุ่มผู้ป่วยวัณโรคที่ติดเชื้อ HIV และกลุ่มผู้ป่วยวัณโรคที่ไม่ทราบสถานะการติดเชื้อ HIV มีสัดส่วนผลการรักษาที่ไม่พึงประสงค์สูงกว่ากลุ่มผู้ป่วยวัณโรคที่ไม่ติดเชื้อ HIV โดยมี relative risks 3.55 (95% CI 2.68-4.69) และ 5.20 (95% CI 3.97-6.81) ตามลำดับ ดังนั้น จึงควรให้บริการให้คำปรึกษาและตรวจเลือดโดยความสมัครใจกับผู้ป่วยวัณโรคทุกราย นอกจากนี้ ควรศึกษาทบทวนกระบวนการดูแลรักษา HIV สำหรับผู้ป่วยวัณโรคทุกรายที่ติดเชื้อ HIV เพื่อหาข้อจำกัดในการดูแลรักษา HIV ต่อไป

**คำสำคัญ:** วัณโรค การรักษาแบบ DOT ไม่ใช้ญาติเป็นพี่เลี้ยง ผลการรักษาที่ไม่พึงประสงค์

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# Factors associated with unfavorable TB treatment outcomes under non-family DOT model: a retrospective cohort study

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## Abstract

This retrospective study aimed to find out factors that might be associated with unfavorable TB treatment outcomes in Thasala Hospital of Nakhon Si Thammarat province, a 120-bed community hospital, where non-family DOT (Directly-Observed Treatment) model for TB treatment has been implemented since 2007. Nine hundred and fifty five new TB patients registered for TB treatment during 2007-2014 were reviewed, but forty-nine patients were excluded mainly due to changed diagnosis. The HIV-positive TB cases and the TB patients with unknown HIV status were more likely to have unfavorable TB treatment outcomes than HIV-negative TB patients. The relative risks were 3.55 (95% confidence interval = 2.68-4.69) and 5.20 (95% confidence interval = 3.97-6.81), respectively. VCT (voluntary counselling and testing) is strongly suggested to provide for all TB cases to get blood HIV testing, and comprehensive HIV care should be reviewed for all HIV-positive TB patients to find-out any existing limitations of HIV care.

**Keywords:** tuberculosis, non-family DOT, unfavorable outcome

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## Introduction

Thailand is one of the 30 high tuberculosis (TB)-burden countries, the 30 high TB/HIV burden countries and the 30 high multi-drug resistant (MDR)-TB burden countries in the world[1]. Even though DOTS (Directly-Observed Treatment, Short-course) has been implemented in Thailand since 1996[2], TB situation seems to be still worsening because the trend of the notified numbers of TB case has been continuously increasing[1]. DOT (Directly-Observed Treatment) – an essential element of DOTS[3] and currently no longer an unresolved issue[4] - has been widely practiced by family member in Thailand[5,6] and might result in non-effective TB treatment outcomes. A non-family DOT model has been developed in upper Southern Thailand since 1999[7], but it has been successfully implemented in very limited areas in Thailand. Thasala Hospital is a community 120-bed hospital in Thasala District of Nakhon Si Thammarat Province of upper Southern Thailand. Its catchment area covered two districts, Thasala District and Nobphitam District, with the total number of population about 155,000 in 2014. The non-family DOT has been implemented in the area of the hospital since 2007. After implementation, the number of new TB cases has been steadily declined year by year. However, in 2014 the reported numbers of new TB case became increasing with unacceptably-high unfavorable treatment outcomes, such as a high death rate. Therefore, factors associated with the unfavorable outcomes needs to be explored to find out solutions to solve the problems.

## Material and Methods

There were three types of new TB cases in the study: pulmonary smear-positive, pulmonary smear-negative, and extra-pulmonary. All of them were started TB treatment with a 6-month TB drug regimen, 2HRZE/4HR (isoniazid, rifampicin, pyrazinamide and ethambutol for the 2-month intensive phase, following by isoniazid and rifampicin for the 4-month continuation phase). The definitions of TB case and treatment outcome were in accordance with WHO (World Health Organization)[3,8].

Unfavorable TB treatment outcomes included died, failure, defaulted and transferred-out outcomes all together, while favorable outcomes were cured combined with completed outcomes.

A retrospective cohort study was planned for data collection and analysis. All new TB patients registered for treatment in TB registration database of Thasala Hospital since the DOTS implementation from the fiscal year 2007 to 2014 (October 1$^{st}$, 2006 to September 30$^{th}$, 2014) were retrospectively reviewed for all recorded pre-treatment factors and then traced forward to determine TB treatment outcomes. Thereafter the data was analyzed prospectively with univariate analysis to obtain relative risks with 95% confident interval (95%CI) for each completely

recorded factor to detect the association with unfavorable treatment outcomes.

The research proposal was approved by the Ethical Review Board of Walailak University (Ethical clearance No. 085/Year 2015)

**Results**

Nine hundred and fifty five new TB patients were registered for treatment of Thasala Hospital in Southern Thailand. However, forty nine patients were excluded due to changed diagnosis to other diseases, such as lung cancers and lung abscess. Among of excluded patients, thirty three patients were smear-negative TB cases and another sixteen patients were extra-pulmonary TB cases. None of smear-positive TB cases was excluded from the study.

The total number of new TB patients registered at Thasala Hospital decreased during 2009-2013, but it became increasing again in 2014 (Table 1). The trend of new pulmonary smear-positive TB patients was also the same with the trend of all new patients. While the new smear-negative TB cases seemed to be steadily decreasing more than half, the extra-pulmonary TB cases looked increasing.

**Table 1** New TB patients registered for TB treatment of Thasala Hospital during 2007-2014

| Patient type/Year | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | Total |
|---|---|---|---|---|---|---|---|---|---|
| Pulmonary, smear+ | 61 | 79 | 83 | 71 | 69 | 59 | 51 | 66 | 539 |
| Pulmonary, smear- | 57 | 53 | 36 | 29 | 23 | 21 | 24 | 20 | 263 |
| Extra pulmonary | 13 | 18 | 21 | 17 | 22 | 15 | 20 | 27 | 153 |
| Total | 131 | 150 | 140 | 117 | 114 | 95 | 95 | 113 | 955 |

Two hundred and thirty two new patients, 25.61%, got unfavorable treatment outcomes, while six hundred and seventy four cases, 74.39%, could get favorable outcomes (Table 2). Among the 232 patients with unfavorable outcomes, 150 deaths made the highest proportion of 64.66%. The detail about actual causes of death was not recorded for all TB deaths.

**Table 2** TB treatment outcomes among new TB patients during 2007-2014

| | Cured | Completed | Died | Failure | Defaulted | Transferred-out | Not evaluated | Total |
|---|---|---|---|---|---|---|---|---|
| Number | 410 | 264 | 150 | 26 | 37 | 19 | 49* | 955 |
| Outcome | Favorable | | Unfavorable | | | | - | Total |
| Number | 674 | | 232 | | | | - | 906 |
| % | 74.39 | | 25.61 | | | | - | 100 |

*Forty nine patients (33 new smear-negative and 16 new extra-pulmonary) were excluded due to no evaluated outcomes

Due to limitation of nature of retrospective cohort design, many factors of interest were absent, or if present, they were usually incompletely recorded. Therefore, there were only four factors with complete records; age, sex, HIV status and type of TB (Table 3).

**Table 3** Associations among various factors with TB treatment outcomes

| Factor | | Treatment outcome | | Total | Incidence | RR | 95%CI |
|---|---|---|---|---|---|---|---|
| | | Unfavorable | Favorable | | | | |
| Age (years) | 15-54 | 142 | 461 | 603 | 0.24 | Ref. | - |
| | 55 or more | 90 | 213 | 303 | 0.30 | 1.26 | 1.01-1.58 |
| Sex | Male | 172 | 489 | 661 | 0.26 | 1.06 | 0.82-1.37 |
| | Female | 60 | 185 | 245 | 0.24 | Ref. | - |
| HIV status | HIV+ | 89 | 129 | 218 | 0.41 | 3.55 | 2.68-4.69 |
| | HIV- | 64 | 492 | 556 | 0.12 | Ref. | - |
| | Unknown | 79 | 53 | 132 | 0.60 | 5.20 | 3.97-6.81 |
| Type of TB | Smear + | 106 | 433 | 539 | 0.20 | Ref. | - |
| | Smear - | 76 | 154 | 230 | 0.33 | 1.68 | 1.31-2.16 |
| | EP | 50 | 87 | 137 | 0.36 | 1.86 | 1.40-2.45 |

EP = extra-pulmonary; RR = relative risk; 95%CI = 95% confidence interval

After the data was analysed with the retrospective cohort design (Table 3), male TB patients had no different with female cases to get unfavorable outcomes, while age groups showed only a slightly statistically significant difference. Older TB patients (55 years old or more) could get a slightly higher chance to have unfavorable outcomes, compared with younger cases (15-54 years old), with the relative risk 1.26. The HIV-positive TB patients and the cases with unknown HIV status had much higher probabilities with statistical significances to get unfavorable outcomes, compared with the HIV-negative TB cases. The relative risks were 3.55 and 5.20, respectively. The pulmonary smear-negative TB patients and the extra-pulmonary TB cases had slightly higher chances with statistical significances to have unfavorable outcomes, compared with the pulmonary smear-positive TB cases. The relative risks were 1.68 and 1.86, respectively.

## Discussion

After Thasala Hospital has implemented the non-family DOT under the DOTS strategy since 2007, the number of new TB patients increased in 2008 (Table 1) as expectedly found in the early stage of DOTS implementation[9]. After 2008, the trend was in decline. However, in 2014, the number of TB cases became increasing again, possibly due to the well-known effective TB services of the hospital. Therefore, TB patients outside the catchment area of the hospital might be willing to come to get TB care at Thasala Hospital. However, it should be investigated for actual reasons.

The number of new pulmonary smear-negative TB patients seemed to be steadily decreasing over period of time, it might result from more competent clinical diagnosis. While extra-pulmonary TB cases looked increasing, that might be due to longer life span of HIV-infected persons from the impact of ARV (anti-retroviral drugs) programme. But all of the possible background mechanisms should be further find out in the hospital.

Unfavorable outcomes found in Thasala Hospital were 25.61% during 2007-2014, that was very closed to 22.6% of a study in Taiwan in 2007-2008[10]. Death was the highest proportion of unfavorable outcomes in Thasala Hospital, with 66.66%, and very closed to 64.2% of a case-control study in Ethiopia in 2012[11]. Death rate of new TB patients in Thasala Hospital, which was 16.56% (150/906, Table 2), was much closed to a study in Tak Province, a province of Northern Thailand, which was 17.1%[12]. However, transferred-out was not included in unsuccessful treatment outcome of the study in Ethiopia. Since death was the very high proportion of unfavorable outcomes in Thasala Hospital, causes of death should be exclusively investigated to plan for death prevention among new TB patients in the future.

Among four factors analysed for the retrospective cohort study, only sex was not different to have unfavorable outcomes. Older TB patients had a higher chance to get unfavorable outcomes, showed the same result as the study in Taiwan, that advanced age was the risk factor for unfavorable outcomes[10]. The older age group might have many co-morbidities that could result in the high death rate. Therefore, causes of death among TB cases should be explored carefully.

The HIV-positive TB patients had a much higher chance to have unfavorable outcomes (RR=3.55; 95%CI 2.68-4.69), compared with the HIV-negative TB cases. The result was the same with the study in Ethiopia in 2012[11]. Therefore, comprehensive care for HIV-positive TB cases should be reviewed to find out any existing limitations or barriers of HIV care in the setting of Thasala Hospital. In addition, TB patients with unknown HIV status in our study had much more likely to get unfavorable outcomes (RR=5.20; 95%CI 3.97-6.81). A recent study in upper Northern Thailand

also found that TB patients with unknown HIV status had the highest death rate compared with TB patients with known HIV status[13]. The average proportions of the new TB patient of Thasala Hospital, who had unknown HIV status, in the most recent years in our study were about 10%. Therefore, strong suggestion is that all TB patients should be provided VCT (voluntary counselling and testing) to reinforce all of them to get blood HIV testing, otherwise, they have a very high chance to get unfavorable TB treatment outcomes, particularly death.

The smear-negative and extra-pulmonary TB patients in our study had a slightly higher risk to get unfavorable outcomes than the smear-positive TB cases. The study in Ethiopia also showed that sputum smear negative treatment category at initiation of treatment was independently associated with increased risk of unsuccessful TB treatment outcome[11]. The smear-negative and extra-pulmonary TB cases may usually be associated with HIV infection and more likely to get unfavorable outcomes, especially death. Thus, HIV status in both groups of TB cases should be more concerned to further provide HIV care. However, the actual proportion of HIV status in both groups should be reviewed, or conducted a further research.

The limitations of retrospective cohort design were incomplete and incorrect data, because all of factors of interest were not planed in advance before conducting the study, and the data was recorded in routine services with uncontrollable way. Therefore, a limited number of factor is usually able to be collected completely for analysis. However, the relative risk can be calculated to find out association with the outcomes we are interested in, rather than the odds ratio. Generally, the relative risk should be a better statistic than the odds ratio. However, the relative risks calculated in our study are only univariate analysis and they might not be true values because of any potentially existing confounders. Therefore, future research with multivariate analysis should be conducted to control confounders to get better results with more accurate relative risks.

## Conclusion

Due to retrospective cohort design, only four factors could be collected for analysis. The TB patients with unknown HIV status and the HIV-positive TB patients had much higher chances to get unfavorable TB treatment outcomes. Therefore, VCT is strongly suggested to provide for all TB patients to get blood HIV testing, and comprehensive HIV care should be carefully reviewed among HIV-positive TB cases to prevent unfavorable TB treatment outcomes, particularly death.

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